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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/556,701	04/24/2000	Hitoo Nishino	0010-1106-0	7992
22850	7590	05/23/2006	EXAMINER	
OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314			KISHORE, GOLLAMUDI S	
			ART UNIT	PAPER NUMBER
			1615	
DATE MAILED: 05/23/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/556,701

Applicant(s)

NISHINO ET AL.

Examiner

Gollamudi S. Kishore, Ph.D

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 15 March 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3,7,8,12,16 and 17 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,7,8,12,16 and 17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

The RCE dated 3-15-06 is acknowledged.

Claims included in the prosecution are 1-3, 7-8, 12 and 16-17.

### ***Claim Rejections - 35 USC § 103***

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 1-3, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas (6,011,019), Hiraide (6,136,862), Nishino (5,849,930) individually or in combination, in further combination with Chein (5,855,920).

Thomas discloses that vasogenic brain edema is the most common edema following brain ischemia and injury and that the antioxidants are effective in the treatment of brain edema by protecting the integrity of the endothelial cells. One of the antioxidants suggested is alpha-tocopherol (abstract, col. 9, lines 32-44, col. 22, lines 10-27). Thomas also suggests liposomes as carriers (col. 10, line 47).

Hiraide teaches that antioxidants relieve cerebral edema by scavenging free radicals generated due to ischemia or cellular injury (col. 1, lines 20 through 59).

Nishino similarly teaches that active oxygen and radicals cause brain edema and antioxidants are used for the treatment. Nishino's invention involves treatment of brain edema by an antioxidant (abstract, col. 1, lines 28-67).

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What is lacking in these references is the use of melatonin.

Chien teaches that melatonin is more powerful antioxidant than vitamins E and C as acting as a free-radical scavenger. Chien also teaches that melatonin also protects against a variety of neurological conditions of brain (col. 4, lines 18-27).

It would have been obvious to one of ordinary skill in the art to use the antioxidant, melatonin for the treatment of brain edema since anti-oxidants are effective against brain edema as evident from Thomas, Hiraide or Nishino and since Chien teaches that melatonin is more powerful than conventional anti-oxidants such as vitamin E and C. The use of liposomes as the delivery vehicles would have been obvious to one of ordinary skill in the art since liposomes are known sustained release vehicles and Thomas is suggestive of the use of liposomes.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Thomas discloses that heat or H<sub>2</sub>O<sub>2</sub> inactivation of super oxide dismutase (SOD), an antioxidant which partially blocks (Fig. 3) vasoconstriction induced by beta-amyloid (Fig. 1), results in partial reduction of the relaxing activity possessed by the SOD on the constriction (Fig. 12). However, according to applicant, Thomas does not disclose anything about a correlation between SOD and any brain disease. With the experimental data provided by Thomas, it cannot be concluded that an antioxidant cures any brain disease. These arguments are not persuasive since on col. 22, lines 10-27 Thomas is clearly **suggestive** of the effectiveness of antioxidants and the treatment of **brain edema**. Applicant's arguments

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that Thomas does not teach the cure of Alzheimer's disease are not pertinent since instant claims are not drawn to this disease.

Applicant's arguments that Hiraide does not disclose anywhere any experimental data that the reduction caused by scavenging free radicals generated due to ischemia or cellular injury. This argument is not found to be persuasive since on col. 1, lines 20-59, Hiraide teaches that the antioxidants relieve cerebral edema by scavenging free radicals generated due to ischemia or cellular injury and melatonin is an antioxidant. Applicant himself has not shown the superiority of melatonin over other free radicals.

Applicant argues that Nishino demonstrates that anti-oxidative activity cannot be correlated even with the reduction of brain moisture are not persuasive since contrary to applicant's arguments, on col. 16, line 30 et seq., Nishino clearly states, " As can be seen from the forgoing examples, the materials belonging to this group has a high DPPH reducing effect (radical-eliminating effect) as well as lipid peroxidation inhibitory activity. Also, the compound of Example 7, for example exhibits an excellent effect of inhibiting both brain infaction and brain edema". Even assuming that there is no correlation between the specific pyroolidine type of antioxidants taught by Nishino, there is a correlation between antioxidants and brain edema as evident from other references cited.

Applicant's arguments that Chien discloses a hormone replacement therapy are not persuasive since irrespective of other teachings, Chien is clearly suggestive of the superiority of melatonin in terms of anti-oxidant activity compared to other antioxidants.

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In essence, the references cited show the effectiveness of anti-oxidants against brain edema and in view of the powerful anti-oxidant effect of melatonin as taught by Chien, one of ordinary skill in the art would be motivated to use melatonin in the treatment of brain edema. Applicant has not shown any unexpected results obtained by using melatonin compared to other antioxidants.

3. Claims 1-3, 7-8, 12 and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas (6,011,019), Hiraide (6,136,862), Nishino (5,849,930) individually or in combination, in further combination with Chein (5,855,920) as set forth above, further in view of WO 97/20555 of record.

The teachings of Thomas, Hiraide, Nishino and Chein have been discussed above.

As discussed before, WO discloses a method of treatment or prevention of ischemic brain injury by administering melatonin. WO also teaches that melatonin is an antioxidant (note the abstract, page 8, lines 10-30, page 9, lines 22-34, page 11, lines 14-16, Examples and claim). WO also teaches the administration of melatonin in the form of emulsions containing hydrophobic phase which is emulsified in an aqueous medium on page 10, line 17 through page 11, line 13 (oil in water emulsions wherein water is the continuous phase). Melatonin is in essence is encapsulated in Oil (matrix) which in turn is surrounded by water which also serves as a matrix.

One of ordinary skill in the art would be motivated further to use melatonin for the treatment of brain edema since the antioxidant with a reasonable expectation of success since melatonin is already known to be used in the treatment of brain ischemia

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as evident from WO 97. WO does not specifically state the composition is a food composition, it teaches the administration of the composition orally using additives and therefore, addition to food for oral consumption is deemed to be within the skill of the art.

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed applicant's arguments regarding Thomas, Hiraide, Nishino and Chien. Applicant provides no specific arguments with regard to WO reference.

4. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas (6,011,019), Hiraide (6,136,862), Nishino (5,849,930) individually or in combination, in further combination with Chein (5,855,920) OR over Thomas (6,011,019), Hiraide (6,136,862), Nishino (5,849,930) individually or in combination, in further combination with Chein (5,855,920) as set forth above, further in view of WO 97/20555 of record as set forth above, further in view of Keller (5,891,465).

The teachings of Thomas, Hiraide, Nishino, WO and Chein have been discussed above. What are lacking in these references are the specific teachings of the use of liposomes as carriers for melatonin.

Keller teaches that the bioavailability of melatonin increases by 33 percent when it is administered in liposomes (abstract, col. 8, line 37 et seq., and examples).

It would have been obvious to one of ordinary skill in the art to use liposomes as carriers for melatonin since Keller teaches increased bioavailability of melatonin when administered in liposomes.

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Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed applicant's arguments regarding Thomas, Hiraide, Nishino and Chien. Applicant provides no specific arguments with regard to WO reference or Keller.

5. Claims 8, 12, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas (6,011,019), Hiraide (6,136,862), Nishino (5,849,930) individually or in combination, in further combination with Chein (5,855,920) OR over Thomas (6,011,019), Hiraide (6,136,862), Nishino (5,849,930) individually or in combination, in further combination with Chein (5,855,920) as set forth above, further in view of WO 97/20555 of record as set forth above, further in view of Wurtman (4,687,763) of record.

The teachings of Thomas, Hiraide, Nishino, Chein and WO have been discussed above. Although WO teaches the administration of melatonin orally, it does not specifically teach that the oral composition be a food composition. It is deemed obvious to one of ordinary skill in the art to administer melatonin in various claimed forms with a reasonable expectation of success, since the reference of Wurtman shows that melatonin is routinely administered as a component of food including a drink, a beverage, a wafer or candy (note the abstract and col. 2, lines 19-59).

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed applicant's arguments regarding Thomas, Hiraide, Nishino and Chien. Applicant provides no specific arguments with regard to WO reference or Wurtman.



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3. This is a continuation of applicant's earlier Application No. 09/556,701. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone

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number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Gollamudi S Kishore, Ph.D  
Primary Examiner  
Art Unit 1615

GSK